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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
10/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,781	YAMASHITA ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2008*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *15-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending. Claims 25-27 were cancelled in Applicants' preliminary amendment submitted 9/12/2005. Claims 15-24 are withdrawn for being drawn to a non-elected invention. **Claims 1-14 are under examination in the instant office action**. Receipt of Applicants claims, 2 IDS (submitted 9/12/05 and 6/10/05), and reply to the restriction requirement submitted on 5/22/08 are acknowledged. This supplemental office action resets the time for reply to the mailing of the instant office action.

Election/Restrictions

Applicant's election of Group I, claims 1-14, in the reply filed on 5/22/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 15-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse[1] in the reply filed on 5/22/08.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The disclosure is objected to because of the following informalities: the abbreviation for mass median aerodynamic diameter, MMAD, is misspelled as MMDA in paragraphs [0213], [0217], [0222], and [0227].

Appropriate correction is required.

The use of the trademark MILLIPORE® in paragraphs [0202], [0209], [0214], [0218], and [0223] has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 6 does not further limit claim 1, because it recites the exact same Markush group of hydrophobic stabilizers.

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[1] Applicants' response was silent as to whether the election was with or without traverse. Thus, the election was

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 8-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 and 14 are vague and indefinite because these claims recite "derivatives of hydrophobic amino acids" (claims 1, 6, and 14), "derivatives of hydrophilic amino acids" (claims 1 and 14), "derivatives of basic amino acids" (claim 3), and/or "derivatives of these amino acids" (claims 2 and 5). Applicants' specification does not define what constitutes a derivative of an amino acid; thus, an ordinary skilled artisan would not be apprised of the metes and bounds of what constitutes a derivative of an amino acid. The 10th edition of the Merriam-Webster's Collegiate Dictionary (Merriam-Webster Incorporated: Springfield, Massachusetts, 1993, pp 311) defines "derivative" as, "a chemical substance related structurally to another substance and theoretically derivable from it." For example, carbon dioxide, water, or nitrogen oxides could theoretically be derived from the combustion of an amino acid. Therefore, the definition of derivative in the Merriam-Webster Collegiate Dictionary does not shed light on what Applicants' intended for the meaning of an amino acid derivative.

Claims 2 and 4-5 are internally inconsistent because said claims recite different Markush groups for the hydrophilic stabilizer than what is recited in parent claim 1. Thus, it is unclear whether the hydrophilic stabilizer should be selected from the Markush group of claim 1, the

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treated as an election without traverse.

Markush group of claims 2, 4, or 5, or from the combination of the Markush groups of claim 1 and claims 2, 4, or 5.

Claim 1 is also indefinite, because the term "fine particle fraction" (FPF) is not defined in the specification to refer to particles having a diameter less than or equal to some maximum value. The art defines fine particle fraction variably, thus, the generic reference to a "fine particle fraction" of at least 10% is indefinite, because the ordinary skilled artisan would be unable to ascertain which particle diameter necessarily defined the upper threshold of the claimed fraction. *See* U.S. Patent Nos. (1) 6,461,591 (FPF is defined as stages 2-8 of an Andersson Impactor, which corresponds to a particle size of ~ 0.43 microns to 9 microns) (col. 11, lines 54-59; Table 1, col. 12, lines 1-20); (2) 6,394,085 indicates that FPF is normally smaller than 6 microns (col. 7, line 12); and (3) 6,284,282 defines FPF as having a aerodynamic mass median diameter of less than 6.8 microns.

The remaining claims are rejected as depending from a rejected claim.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Yamashita et al. (US 2003/0101995).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Applicants claim a freeze-dried composition comprising (i) interferon-gamma, (ii) at least one hydrophobic stabilizer selected from a group including hydrophobic amino acids and derivatives of hydrophobic amino acids, and (iii) at least one hydrophilic stabilizer selected from the group including hydrophilic amino acid derivatives.

Yamashita discloses the same dry powder inhalation system as claimed by Applicants, in Yamashita's Figure 1 and exemplified, for example, in Examples 27-37 [0443]-[0446] (see also Table 3 in [0437]). The disintegration indices of the non-powder solids contained in the vessel of the dry powder inhalation system of Figure 1 and exemplified in Examples 27-37 are all greater than 0.05 (in fact, higher than 0.1). The non-powder solids utilized in the examples were characterized as being **cake-like** [0443] and **were prepared by freeze-drying liquid compositions of interferon-gamma admixed with hydrophobic (Examples 27-31), hydrophilic stabilizers, or mixtures thereof (Examples 32-36)**. Application of an air jet with an **air velocity of 35 m/sec and an air flow rate of 40 ml/sec** resulted in aerosolized fine particles characterized by **a MMAD of much less than 10 microns (all had a MMAD between about 1.2 and about 1.8 microns) and a fine particle fraction greater than approximately 45% (Examples 32-36)**.

Yamashita also discloses that a more preferred disintegration index is 0.05 or more [0154]. The components of the dry powder inhalation system of Figure 1 are described in [0071]-[0072] and include **a vessel, stopper, freeze-dried composition**, **air jet flow path,**

discharge flow path, needle part, inhalation port, air intake member, tubular safety cover, air pressure-feeding means, bellow body, intake valve, intake port, discharge valve, discharge port, connecting port. The functioning of Yamashita's invented dry powder inhalation system is described in [0127]-[0129]. It is noted that in Examples 32-35, **the hydrophilic stabilizer is present in an amount ranging from 8.3-20 parts by weight per 100 parts by weight of the hydrophobic stabilizer**.

Claims 1-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Yamashita et al. (US 2003/0101995)

The applied reference has a common assignee (i.e. Otsuka Pharmaceuticals) and some common inventors (i.e. Yamashita, Akagi, and Fukunaga) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Applicants' claims have been described above. The disclosures of Yamashita have been set forth above. Applicants' claims are anticipated by Yamashita as set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP-61044826 (English abstract only; "JP-826") in view of JP 59-181224 (English Abstract only; IDS reference; "JP-224") and Tober et al. ("Structural features of interferon-gamma aggregation," Protein Science, 2002 June, 11(6), 1340-1352).

Applicant Claims

Applicants claim a freeze-dried composition comprising (i) interferon-gamma, (ii) at least one hydrophobic stabilizer selected from a group including hydrophobic amino acids and derivatives of hydrophobic amino acids, and (iii) at least one hydrophilic stabilizer selected from the group including hydrophilic amino acid derivatives.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

JP-826 teaches a **freeze-dried interferon-gamma composition** comprising an amino acid (e.g. **monoamino-aliphatic amino acid**) having a decreased inorganic salt concentration (preferably below 0.05M). The term "monoamino-aliphatic amino acid" reads on a hydrophobic amino acid, as well as on hydrophobic amino acid derivatives. Per Applicants' definition in paragraph [0110] of the specification, any freeze-dried interferon-gamma composition necessarily has a non-powder cake-like form.

JP-224 teaches stabilize freeze-dried interferon preparation comprising human serum albumin and an amino acid, wherein the **human serum albumin is present in an amount of 0.01% w/v** and **the amino acid is preferably present in an amount of 0.05% w/v**. JP-224 teaches that any amino acid can be used, but that particularly effective amino acids include polar amino acids, such as arginine, lysine, serine, threonine, etc. Per Applicants' definition in paragraph [0110] of the specification, any freeze-dried interferon-gamma composition necessarily has a non-powder cake-like form.

Tober teaches that interferon-gamma is susceptible to denaturing and aggregation under a variety of conditions, such as high temperature, low pH, and in the presence of chaotropes (pg. 1341, right column, 1st full paragraph in right column).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

JP-826 lacks the teaching of freeze-dried interferon compositions comprising hydrophilic stabilizers. This deficiency is cured by the teachings of JP-224. JP-826 is silent regarding the teaching of a disintegration index and the effect of an air impact with a speed of at least 1 m/sec and an air flow rate of at least 17 ml/sec.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to combine the teachings of JP-826 and JP-224 at the time of Applicants' invention, because interferon-gamma is known to be unstable under various conditions (Tober). An ordinary skilled artisan would have been motivated to include serum albumin and amino acid stabilizers in the formulation of JP-826 to stabilize interferon-gamma, because interferon gamma is known to be susceptible to denaturation under various conditions. An ordinary skilled artisan would have had a reasonable expectation of stabilizing interferon-gamma in the formulations of JP-826, because JP-224 teaches that amino acids in combination with serum albumin result in stabilized interferon preparations. Regarding the disintegration index, because the combined prior art teach substantially similar composition to what Applicants' are claiming this property is necessarily present. It is also noted that the term

disintegration index is not a term of art in the pharmaceutical art, but rather is a term invented by Applicants and defined in paragraph [0112] of Applicants' disclosure. It is noted that serum albumin reads on a derivative of any amino acid, including hydrophobic amino acid derivatives, which are kind of hydrophobic stabilizer recited in Applicants' claim 1. The ratio of serum albumin and amino acid recited in JP-224 falls within the range of the ratio recite in Applicants' claim 8. In addition, the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Upon optimization of the amounts of albumin and amino acid, the compositions of the prior art would optimize the ratio of hydrophilic and hydrophobic stabilizers.

Regarding property (iv) of Applicants' claim 1 and Applicants' dependent claims 11-13, this property is necessarily present because the combined prior art teaches essentially the same formulation claimed by Applicants. Thus, it is a reasonable to conclude that property (iv) is present in the formulations of the combined prior art. Finally, concerning the selection of valine, leucine, isoleucine, or phenylalanine as the hydrophobic stabilizer, an ordinary skilled artisan would have been motivated to try different amino acids as stabilizers; because JP-224 teaches that any amino acid is suitable and valine, leucine, isoleucine, or phenylalanine are among the 20 naturally occurring and common amino acids. Applicants have made no allegations of surprising

or unexpected results in their specification. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. The instant rejection is deemed to be proper.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The following references are considered relevant because these references teach freeze-dried interferon compositions comprising amino acids: Terano (US Patent No. 4,659,570) and Kato et al. (U.S. Patent No. 4,675,183).

Claims 1-14 are rejected. Claim 6 is objected. Claims 15-24 are withdrawn from consideration. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/James H Alstrum-Acevedo/
Patent Examiner, Art Unit 1616
Technology Center 1600